EFFECTS OF ARTIFICIALLY INDUCED PAIRED AND COUPLED BEATS*

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Introduction

The recent preliminary report made by Lopez, Edelist, and myself at the October 1963 meeting of the American Heart Association in Los Angeles[1] led to a series of reports on the effects upon the heart's performance of paired artificial pacing of the ventricles or atria, and of coupling an artificial pacemaker with the natural one of the heart.[2-4] The modifications of the heart action involve a reduced frequency of the *effective* ventricular beats and/or an increase of their strength. It was, and is, hoped that with this approach the pumping ability of the heart would be significantly improved in either one or both of these ways, without incurring any untoward reactions.

I propose to review some of the benefits and hazards that may be expected with paired and coupled pacing, and to consider some of the mechanisms involved. I shall make use of unpublished studies of my department as well as those already reported by us. My colleagues, Drs. R. Langendorf, A. Pick, and L. J. Hirsch will contribute separately to this symposium on further aspects of this subject. There will not be sufficient time to deal as extensively with the work of other groups, and this is unnecessary since they are well represented at this symposium.

Much of the knowledge upon which this symposium is predicated is long-standing although the ultimate basic mechanisms giving rise to them are not clearly established in all instances, especially at the cellular and molecular levels. One of the important by-products of this surge of interest will be to enhance this basic knowledge. Another, hopefully, will be the acquisition of an added tool to make the heart a better pump. It will be necessary to define clearly and with some pre-

* Presented at the Conference on Paired Pulse Stimulation and Postextrasystolic Potentiation in the Heart, held at The New York Academy of Medicine, January 13, 1965. The work upon which this report is based was supported in part by Grant HE-06375 of the National Heart Institute, Bethesda, Md.

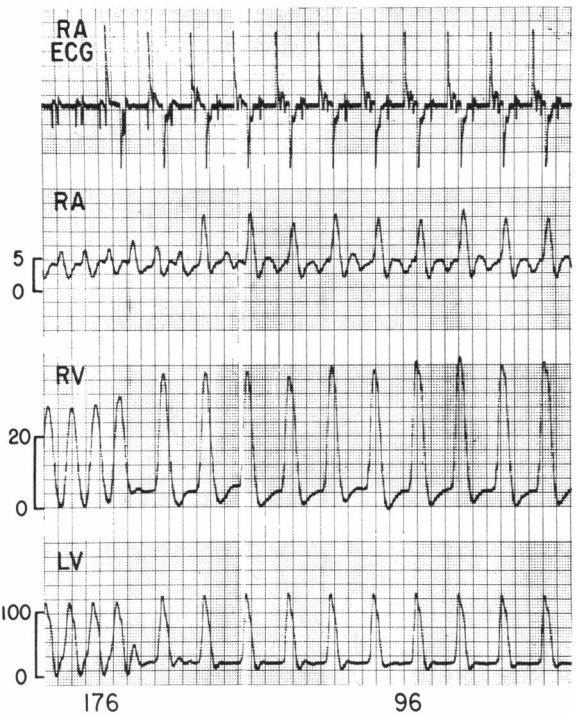

Fig. 1. Effect of paired stimuli on heart rate and on right atrial (RA), right ventricular (RV) and left ventricular (LV) pressure curves of the dog. Long artificial electrical pulses, applied to the right ventricle, were started after the third beat, giving rise to make and break stimuli (shown by large artefacts in the electrocardiographic tracing). The ventricles were captured by these paired impulses but only the make gave rise to an *effective* ventricular beat leading to a slowing in the effective heart rate (from 176 to 96/min.) and to an enhancement of these beats (taken from Figure 3 of Lopez *et al.*[2]). The break led to an ineffective beat. RA ECG is a unipolar intracavitary right atrial electrocardiogram. Pressure scales are in mm. Hg. Discussed in text.

cision the indications and contraindications for the use of artificially paired and coupled beats clinically so that the use of this approach may be placed on a rational basis and its hazards minimized.

Suffice to say at the outset that this method of inducing grouped beating of the heart is still experimental and not yet ready for widespread everyday clinical use. There is still some hazard in connection with this approach. In a severely impaired heart this procedure may lead to heart failure or ventricular paroxysmal tachycardia and ventricular fibrillation. In the presence of ischemic heart disease, there may also be some aggravation of the ischemic state with the development or extension of myocardial infarction. Even in a more normal heart, the

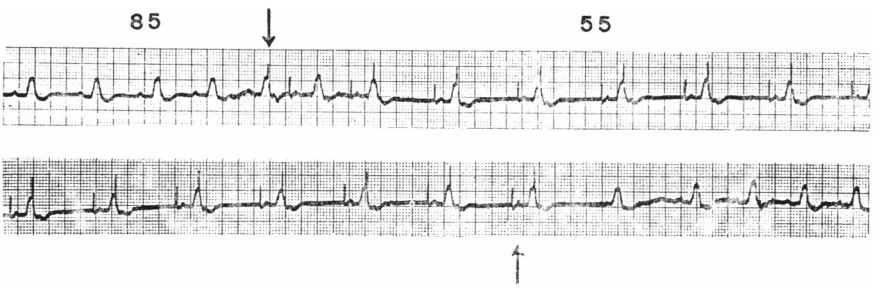

Fig. 2. Lead II of the electrocardiogram of a patient who had a pacemaker inserted intravenously to control Stokes-Adams attacks due to intermittent A-V block. The electrodes at the time the record was taken were temporarily moved into the right atrium. Paired electrical pulses (shown by artefacts) were used between arrows, and they captured the atria. However, only the 1st of each pair reached the ventricles, the second being stopped in the A-V junction. As a consequence, the ventricular rate (both electrical and mechanical) was slowed from 85 to 55/min. (from Figure 9 of Lopez *et al.*[2]). Discussed in text.

danger of repetitive responses leading to paroxysmal tachycardia and fibrillation still exists. My plea at this time is that this procedure be used with extreme caution exclusively by the most experienced cardiologists, and only when the indications are clear and the possibility of undesired complications minimal or nonexistent.

We are still in a period of trial and error with this approach, a period that doubtless will be short-lived as further careful studies establish its clinical place and give better insight into the basic mechanisms involved in both the normal and diseased heart.

In this presentation I shall consider the subject in the following order: 1) mechanisms involved in altering impulse initiation and conduction; 2) mechanisms involved in producing the ineffective beat; 3) mechanisms involved in enhancing the effective beat; 4) alterations in O_2 consumption of the heart in paired and coupled beats; 5) alterations in coronary flow in paired and coupled beats; and 6) possible benefits to be derived from the use of paired and coupled beats.

Mechanisms Involved in Altering Impulse Initiation and Conduction

When we began this work we made use of long electrical pulses, the make and break of which served as the paired stimuli to produce the effect sought (Figure 1). Later, pairs of short electrical pulses (3 msec. in duration) were substituted. The stimulating electrodes were applied to the atria or ventricles of the dog. Such stimulation was found to be

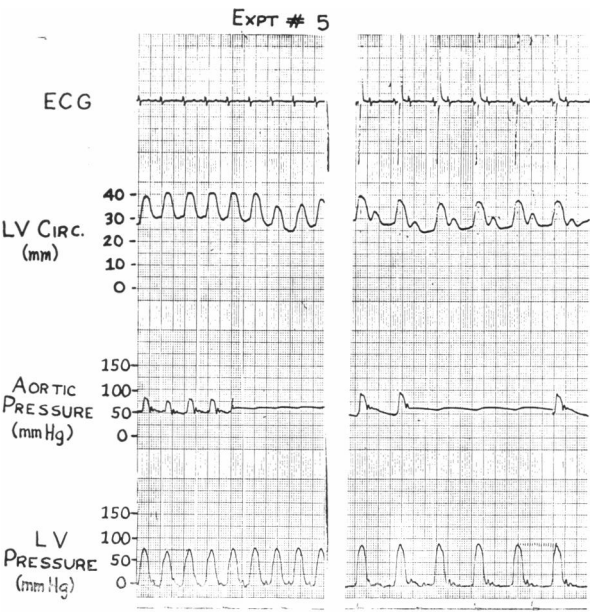

Fig. 3. The experiment was done on a right heart bypass preparation of the dog in which the left ventricular minute-input was kept constant (unpublished experiment of L. J. Hirsch and L. N. Katz). Left panel shows control of heart by sinus rhythm (rate 158/min.); that on the right, when a brief artificial electrical impulse applied to the right ventricle (shown by large artefacts in ECG) was coupled to every sinus impulse. This artificial impulse gave rise to a ventricular electrical response and to an ineffective beat as shown by the small response in the LV circumferential mercury gauge (LV Circ.), the tiny response in the LV pressure pulse and the absence of response in the aortic pressure curve. (The horizontal stretches in the latter are intervals when mean aortic pressure was obtained.) The artificial impulse also traversed the A-V junction in a retrograde fashion, entered the sinus node and slowed the frequency of firing of the sinus pacemaker (to 91/min.). This combination of coupled beating permits the atrial systole to maintain its contribution to ventricular filling in the effective beats. The pressure amplitude and systolic peak pressure (and dp/dt) of the effective beats were enhanced in both the left ventricle and aorta. However, the duration of the LV pressure curve of these beats was shortened. ECG is lead II. Discussed in text.

effective for as long as 24 hours.[2] The same technique of paired electrical pulses was used in our first human case employing an intravenous pacemaker inserted into the right atrium (Figure 2). Such pairs of stimuli, when effective, result in either atrial or ventricular bigeminy, or bigeminy in both chambers.

Bigeminy can also be produced by an artificial pacemaker when its frequency is the same as that of the natural pacemaker but its time of discharge is out of phase (Figure 3). This gives rise to artificially coupled beating. In this particular case, the artificial ventricular impulse traveled backward through the A-V junction and penetrated to the sinus pacemaker and so altered the frequency of the sinus firing.

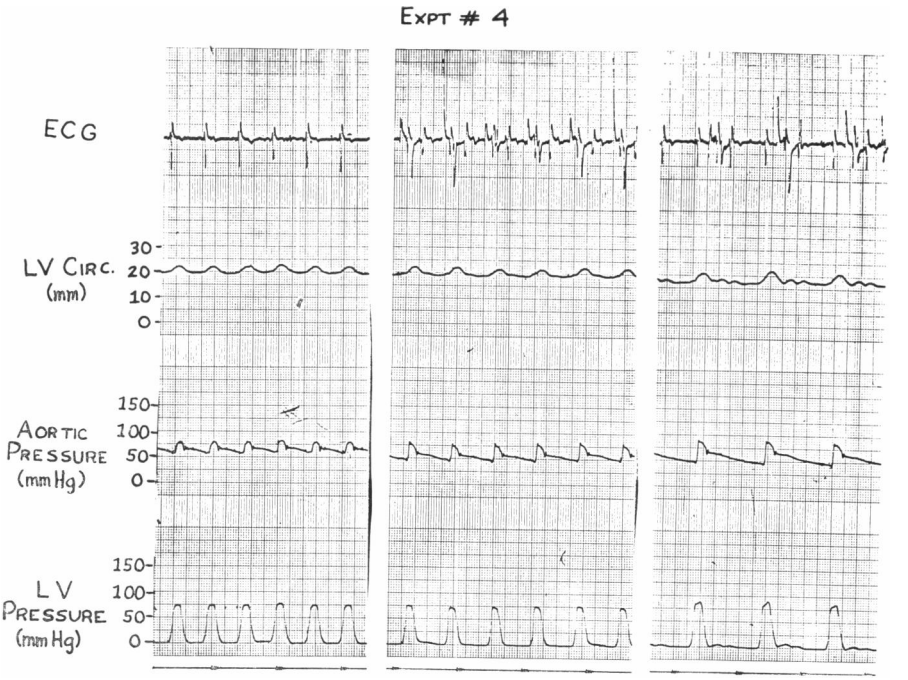

Fig. 4. Another experiment in the same type of preparation as in Figure 3 (from unpublished work of L. J. Hirsch and L. N. Katz). Conventions as in Figure 3. Left panel shows control by sinus rhythm (115/min.). Middle panel shows capture of ventricles by paired artificial electrical stimuli, make and break (shown by artefacts in ECG) applied to the right ventricle. As in Figure 1, only the make produced an effective beat (slowing the effective heart rate 91/min.), the beat induced by the break was ineffective, causing no response in the aortic pressure curve and only a tiny one in the left ventricular pressure curve and circumferential gauge. The amplitude of the effective ventricular beat is not increased nor is its systolic pressure. However, dp/dt in both the left ventricular and aortic pressure curves are increased and so is the amplitude of the aortic pulse. The duration of the ventricular pressure curve is shortened. In the right panel, a slower frequency of the artificial pulses was used giving rise to make and break stimuli, with the result that the paired stimuli that controlled the ventricles were coupled to every second sinus impulse, the alternate sinus impulses being stopped at the A-V junction. Only the conducted sinus impulses produced effective ventricular beats (rate 57/min.), the other two beats of the ventricular trigeminy, due to the paired artificial stimuli, were ineffective in that they do not appear on the aortic pulse but cause minor deflections in the left ventricular pressure pulse and circumferential gauge. The effective beats show increased amplitude, systolic pressure, and dp/dt when compared to the control. Discussed in text.

When paired stimuli are applied to one of the ventricles they take over control of the ventricles and ordinarily lead to a complete A-V dissociation. Hence the natural supraventricular impulses do not pass the A-V junction. This arrangement, however, requires that there be, within certain limits, for any frequency of the natural pacemaker, a definite frequency of the paired stimuli and a definite interval between the two stimuli of the pair. Only when the limits in this relationship

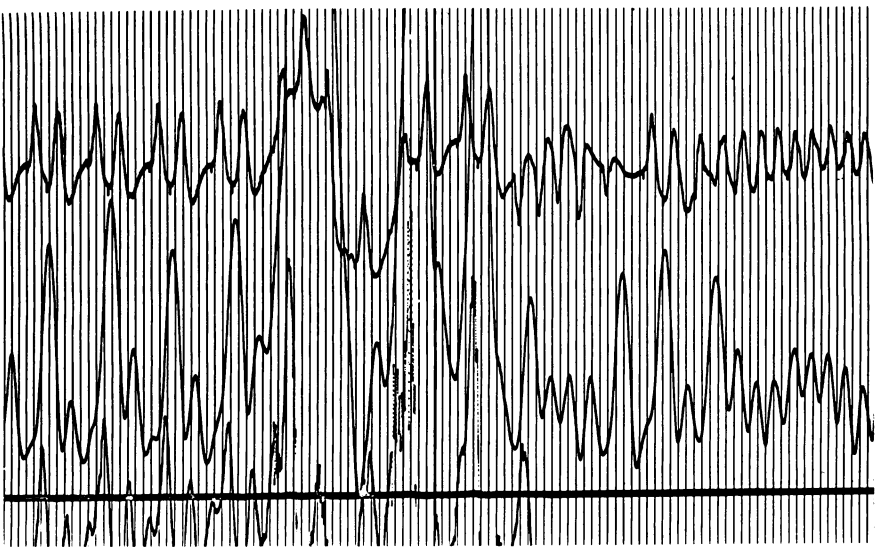

Fig. 5. Record of lead 2 of electrocardiogram *(above)* and right ventricular pressure pulse *(below)*—disregard trace crossing base line—in a patient in severe congestive heart failure, showing effect of paired ventricular pacing (unpublished case of A. Shaffer, M. Luria and R. Langendorf). The paired stimuli applied to the right ventricle captured the ventricles in the first part of the record. The alternation between effective and early ineffective ventricular beats are clearly seen. In the middle of the record the patient had a coughing spell (shown by the large swings of the traces). Immediately after this spell, the second of the pair of impulses is followed by a run of 5 repetitive ventricular beats (a paroxysmal ventricular tachycardia), the first and last of which have small effective ventricular beats. This run is followed by a pair of ventricular responses to the artificial pair of stimuli, followed in turn by a run of repetitive ventricular beats, which, except for the first, give rise to ineffective ventricular beats. Ventricular fibrillation terminated this run (not shown). The fibrillation was terminated, and control by the sinus pacemaker was established by stopping the paired pacing and then using a countershock. Discussed in text.

among these three variables are not exceeded will a reduction in frequency of the effective ventricular beats occur.

On occasion, in the case of ventricular application of the artificial pacemaker generating paired impulses, the ventricular impulses will pass through the A-V junction into the atria and enter the S-A node to keep the natural pacemaker suppressed. Atrial stimulation with paired impulses could lead to a similar effect on the sinus node. When paired stimulation effectively controls the atria in the presence of an ectopic atrial rhythm, the mechanism involved would be the same, and a similar mechanism would also apply when paired stimulation becomes effective in wresting away control of the ventricles from a natural ectopic ventricular pacemaker. Only when the natural ventricular pacemaker is parasystolic in character will paired ventricular stimulation induce a

complete intraventricular dissociation (cf. Figure 11 of Lopez *et al.*[2]).

The A-V dissociation with paired impulses may be incomplete. This result could be due to regular captures of atria and/or ventricles by the natural pacemaker. Thus in the right-hand panel of Figure 4, the paired artificial ventricular impulses only prevent every second sinus impulse from capturing the ventricles. The result in this case is a trigeminy. Similarly, a bigeminy would result when an artificial ventricular pacemaker is coupled to the ventricular beats of a supraventricular rhythm so as to prevent every other natural impulse from capturing the ventricles.

Another instance of incomplete A-V dissociation (in man) with regular captures of the ventricles is shown in Figure 2, obtained by the use of atrial paired stimulation which captured the atria. The second of the pair of stimuli did not capture the ventricles because they reached the A-V junction while it was still refractory from the effect of the first.

Regular ventricular captures in incomplete A-V dissociation are not ordinarily hazardous, but irregular captures may be, leading as they can to repetitive reponses and intermittent tachycardia and, ultimately, to fibrillation. Figure 5 is such an example in a clinical case with severe congestive heart failure and low cardiac output. In this patient a paroxysm of coughing during use of effective paired pacing led to repetitive responses and then to ventricular fibrillation, which was converted to sinus rhythm by stopping the pacemaker and using countershock.

Such periods of irregular ventricular captures can occur especially during the inception of pacing or when, for one reason or another, the heart fails to respond to one or more of the artificial impulses. It is at such times that the risk of ventricular fibrillation is ever present.

Closely allied to the foregoing hazard during inception of pacing is the occurrence of the coupled artificial impulse near the end of the absolute refractory phase of the preceding response. Under these circumstances, one or more of these impulses may fail to capture the heart, thereby setting up conditions favorable for repetitive responses, provided that, at the same time, some of the next impulses that reach the ventricles occur in the vulnerable phase.

These problems are not peculiar to artificial paired and coupled stimulation, they can occur with ordinary single-impulse artificial pacing. But the fact that paired and coupled pacing is ordinarily employed

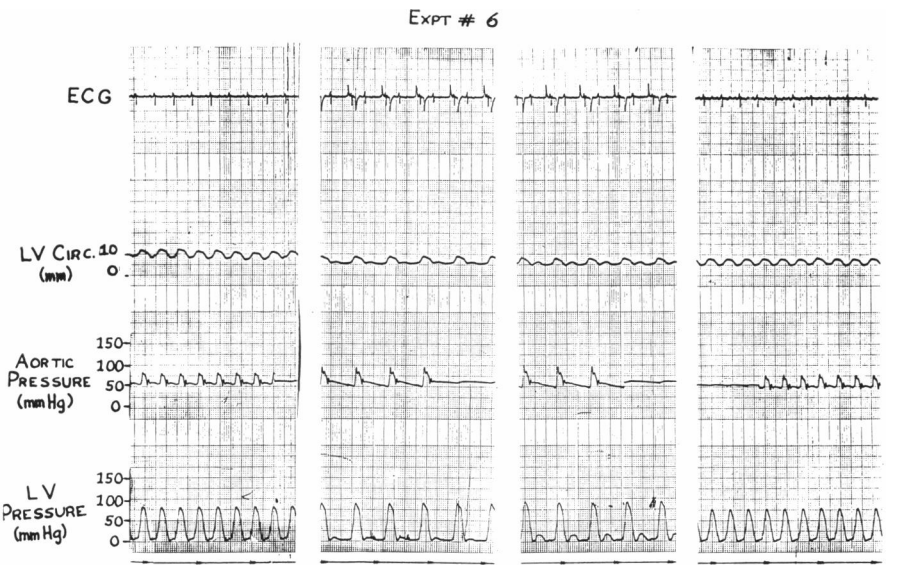

Fig. 6. Another experiment in the same type of preparation as in Figure 3 (from unpublished work of L. J. Hirsch and L. N. Katz). Conventions as in Figure 3. Left panel shows sinus rhythm (167/min.). Next two panels show paired electrical stimuli (make and break) controlling the ventricles and giving rise to alternate effective and premature ineffective beats (the rate of the effective beats is, respectively, 125 and 120/min.). In the second panel the prematurity of the ineffective beat is more marked than in the third panel and, as a result, the ineffective beat is smaller in the former in the LV pressure and circumferential gauge. The last panel on the right shows the sinus pacemaker again in control (167/min.) when the artificial pacemaker is turned off. Discussed in text.

in more diseased hearts than is single pacing increases the hazard of such repetitive responses.

Other aspects of this phase of the subject are discussed by Drs. Pick and Langendorf of my department.

Mechanisms Involved in Producing the Ineffective Beat

In producing a reduction of the frequency of the ventricles one of two events may take place:

1) In the case of atrial stimulation, the coupled impulse fails to reach the ventricles so that they remain quiescent at this time and neither an electrical (QRST) nor a mechanical response occurs (Figure 2).

2) However, in atrial stimulation, there may be an electrical response of the ventricles to the coupled impulse but the beat occurs so early in the cycle as to lead to a diminished mechanical response. This is the case also when such ventricular stimulation is employed.

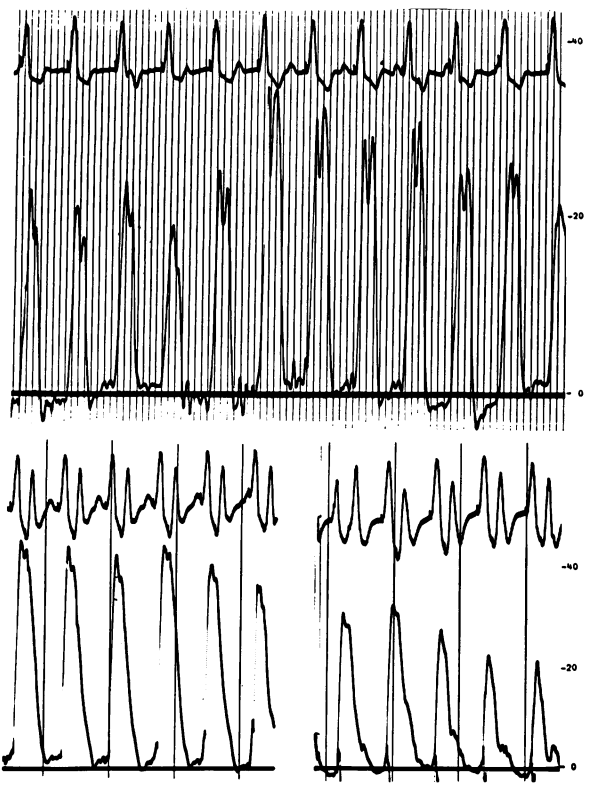

Fig. 7. A comparison of single (upper panel) and paired ventricular pacing (lower panel) in a case of comlete A-V dissociation with advanced A-V block (from unpublished work of A. Shaffer, M. Luria, and R. Langendorf). In each panel the electrocardiogram, lead II, is above and the right ventricular pressure below, the scale is at the right (in mm. Hg.). Note that the sensitivity of the transducer in the upper panel was twice that in the lower. The speed of the paper is the same in both panels. The major variations in magnitude of the right ventricular pressure pulse in the upper panel is due to the timing of the atrial systole (cf. P waves in ECG). The amplitude of the ventricular pressure pulse is greatest in beats where the atrial contribution is most effective, and it is smallest where the atrial contribution is ineffective. The intermediate beats represent the effect of partially effective atrial contributions. Not only is the amplitude of the pressure pulse varied but its duration as well. In the lower panel, the basic change in right ventricular pressure amplitude and duration is the same as above, but there is, in addition, a variable amount of postextrasystolic potentiation due to the fact that, despite the fixed coupling of the pair of impulses, the variation in duration of the effective beat, depending on the effectiveness of the atrial contribution, makes the ineffective beat come at different times on the descent of the preceding pressure curves. In large beats it merges almost completely with the descent; in small beats it is seen as a distinct wave. Hence in paired stimulation, as compared to single stimulation, varying potentiation due to positioning of the premature ineffective beat enhances the effect of the augmentation due to atrial contribution. Discussed in text.

When the stimulus falls early in the rapid inflow phase, ventricular filling becomes inadequate and, consequently, the beat does not create enough intracavitary pressure to exceed that in the aorta or pulmonary artery, and ejection does not occur. Consequently no evidence of a pulse appears at this time in these exit vessels. This small beat is an ineffective beat in that it fails to perform the task of the ventricle, namely, to eject blood. The ventricle contracts isovolumically, without change of volume, but not isometrically inasmuch as it changes in shape —decreasing its apex to base diameter and enlarging its waist. The size of the ventricular pressure pulse will decrease the earlier the contraction occurs in the rapid inflow phase, until it is lost in the foot of the pressure fall of the preceding ventricular beat. These facts are shown in the dog (Figures 4 and 6) and have been reported in man (cf. Braunwald,[5] and is shown in Figure 7, bottom left).

Such ineffective ventricular beats occur also with natural premature beats of various sorts in man (Figures 9 and 10) and have been described in alternans in the dog by us.[8]

In coupled or paired artificial pacing, the premature response of the ventricle may occur before rapid filling begins; that is, during the phase of isovolumic (not isometric) relaxation. Isovolumic relaxation of the ventricles is a phase where ventricular volume does not change while ventricular pressure is falling—a fall, incidentally, that continues into the rapid inflow phase. While volume does not change during isovolumic relaxation, the shape of the ventricle does change—the apex-base diameter lengthens and the waist narrows. A premature contraction occurring at this time also is isovolumic, but it tends to reverse the change in shape that otherwise would occur in isovolumic relaxation; namely it leads: 1) to a lessening of the apex to base elongation or even reverses it and causes a shortening, and 2) it lessens the waist narrowing or even causes the waist to enlarge. These effects will lead to a disparity between the pressure curve of the ventricle and the strain gauge record or that from a circumferential gauge (Figures 3, 4, 6, and 11). Dr. Hirsch discusses this aspect of the subject further during this symposium.

A similar sharp reduction of the coupled beat occurs in the isovolumic preparation of the left ventricle in the right heart bypass set-up of the dog in which the left heart ejects no blood (Figure 12).

It is an error to assume that when the ejecting ventricle is stimulated during the isovolumic relaxation phase it does not contract. The change

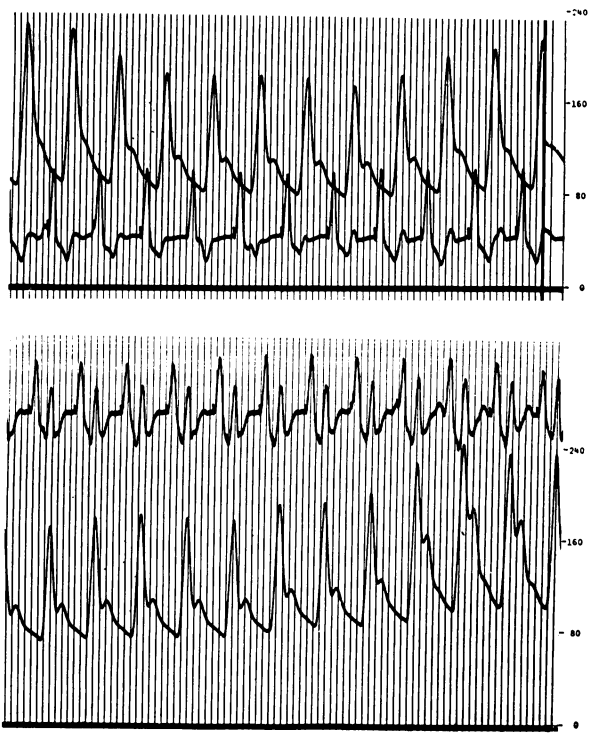

Fig. 8. A comparison of single (upper panel) and paired (lower panel) ventricular pacing in same case as shown in Figure 7. In each panel the electrocardiogram (lead II) and the brachial pressure pulse is shown; in the upper panel, the brachial pressure pulse is above, in the lower it is below. Scale on right is in mm. Hg. The change in systolic, diastolic, and pulse pressure in each panel is clearly related to the proper timing of the atrial systole (cf. P waves in ECG). When atrial systole comes to lie closer and closer to the onset of ventricular systole, up to a point, so as to be more and more effective, the pressure parameters rise. As in Figure 7, the increase in these pressures so produced is greater in the presence of paired than with single pacing, and for the same reason. Discussed in legend of Figure 7 and in text.

in intracavitary pressure may not be measurable at times, but properly placed circumference or strain gauges will demonstrate changes indicating that there is an isovolumic but not an isometric contraction at this time. If it is early enough it will also be isobaric. The fact that contraction does occur is important because every contraction of the ventricles is accompanied by energy release, small as it may be, and by consumption of oxygen by the heart (see below).

Mechanisms Involved in Enhancing the Effective Beat

Three major influences may be said to enhance the magnitude of the effective beat: 1) the initial volume, 2) the afterload, and 3) the

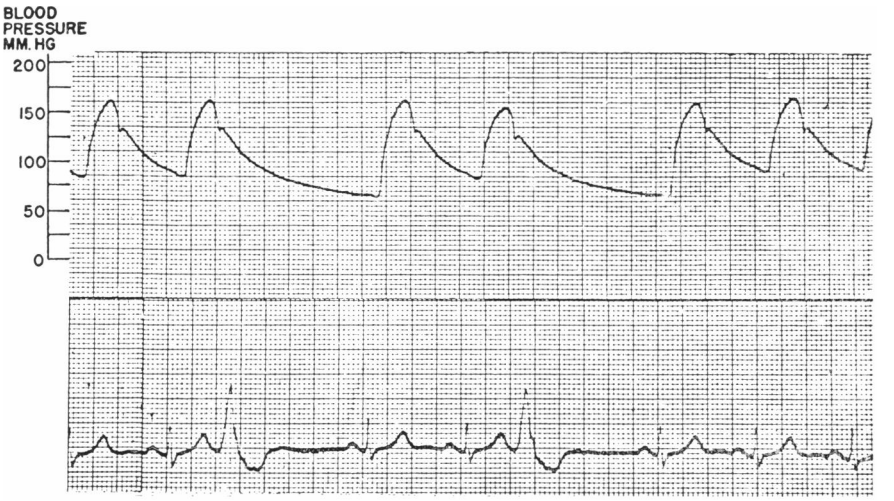

Fig. 9. Intermittence of the aortic pressure pulse in man caused by premature ventricular systoles that cause ineffective ventricular beats (from Figure 69 of Katz and Pick[7]). The aortic pressure (above) was obtained by retrograde catheterization of the aortic arch. On auscultation, a first heart sound occurred during the pulse intermittence but not a second heart sound. Discussed in text.

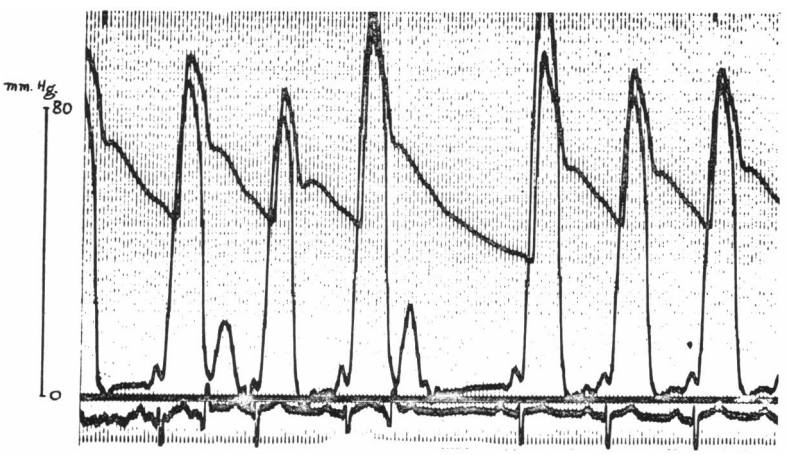

Fig. 10. Effect of naturally occurring ectopic premature beats (second and fourth of the electrocardiogram [lead II], shown below) upon right ventricular and brachial pressure pulses in man (unpublished case of A. Shaffer). Both are premature ventricular systoles. They give rise to ineffective ventricular contractions, showing small pulses in the right ventricular pressure curve and none in the brachial. The first is interpolated, and the postextrasystolic beat that follows shows smaller pulses in both the right and left side of the heart. However, the next beat after this shows greater enhancement of size (including the atrial wave that precedes it). The postextrasystolic beat following the second premature systole shows similar enhancement. Discussed in text.

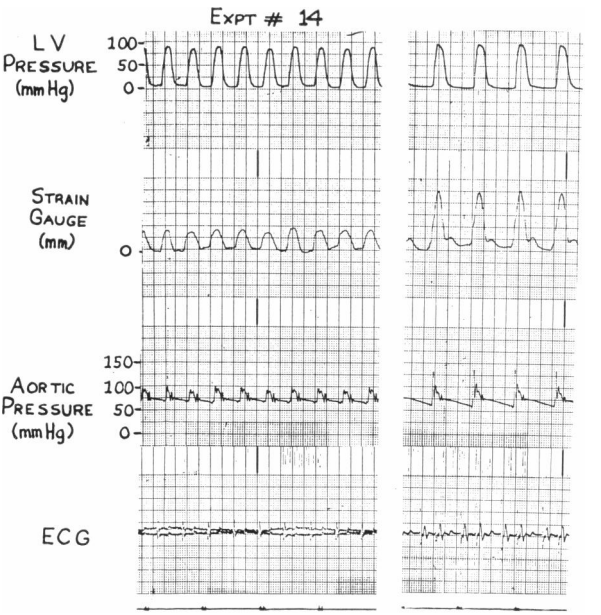

Fig. 11. Another experiment in the same type of preparation as in Figure 3 (from unpublished work of L. J. Hirsch and L. N. Katz). In this case a Minneapolis-Honeywell strain gauge was used instead of the circumferential gauge as in previous experiments; otherwise the conventions and the arrangements are as in Figure 3. Sinus rhythm (rate 136/min.) is shown in left panel, paired pacing in the right. The paired stimuli captured the ventricles leading to an effective beating of the ventricles at a rate of 88/min. The premature impulses give rise to ineffective beats clearly visible in the strain gauge but not in the left ventricular pressure curve (nor in the aortic). In the effective beats dp/dt is increased. Discussed in text.

interval elapsing after the preceding beat. There is some overlap since each of these, in the intact animal, may modify the others. Besides, there are others that may be involved to a lesser degree, particularly neurogenic and humoral influences, which act on the myocardium over and above any influence they may have by way of the three factors just mentioned.

The effect of initial load in increasing the size of the ventricular contraction will be called *augmentation*. This augmentation depends on the Frank-Starling law. It is set by the end-diastolic volume of the ventricle; the latter, in turn, depends (among other things) chiefly upon the filling time, the filling pressure, and the magnitude of the atrial contribution. The upper panel of Figures 7 and 8 (taken from unpublished work of Shaffer, Luria, and Langendorf of my department) show such an augmentation effect on the brachial and right ventricular pres-

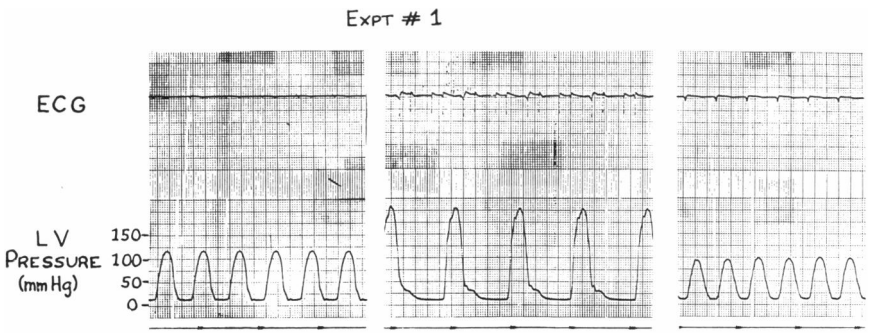

Fig. 12. Observations made in right heart bypass preparation of the dog in which the left ventricle was made isovolumic so that it discharged no blood (for description of preparation see Lendrum *et al.*[9]). (Unpublished work of L. J. Hirsch and L. N. Katz.) The volume of the left ventricle, therefore, remained constant during the heart cycle and was the same in all three panels. The panels on the left and right show sinus rhythm, the one in the center the effect of capture of the ventricles by the paired stimuli from an artificial pacemaker applied to the right ventricle. The sinus rate before and after paired pacing was, respectively, 100/min. and 111/min. The rate of the paired beats when the artificial pacemaker was on was 60/min. None of the beats were effective since the left ventricle discharged no blood into the aorta; they were all isovolumic. The second stimulus of the pair produced a small contraction, seen to take off from the foot of the first, which was greatly enhanced in magnitude and in dp/dt. Since volume was constant in this ventricle, and no filling or emptying of this chamber took place, the changes in the pressure pulse clearly reveal potentiation (as defined in this report). Incidentally, the difference in height of the pressure pulse between the panels on the right and left, associated with a difference in heart rate, represent rest-potentiation. Discussed in text.

sure pulses in a case of complete A-V dissociation in advanced A-V block induced by single artificial pacing applied to the ventricles. As the atrial systole shifts in the ventricular cycle from beat to beat, the artial contribution to filling varies, and this leads to the change in pulse amplitude and diastolic level in both the arterial and ventricular pressure pulses; also, it alters the duration of the ventricular pressure pulse. The enlargement of the pressure pulses represents augmentation (due to increased initial volume).

A similar augmentation of the left ventricle of the dog is shown in Figure 13 due to changes in initial volume in a right heart bypass preparation in which the left ventricle is made to contract isovolumically by filling its cavity with a saline-filled balloon.[9] The left ventricle in this preparation does not eject blood (and the right ventricle is hypodynamic and contracts almost isobarically in ejecting the coronary blood flow). As the ventricular volume is elevated by distending the balloon within it, the pressure pulse increases in height and duration.

Augmentation due to increase in afterload comes about primarily

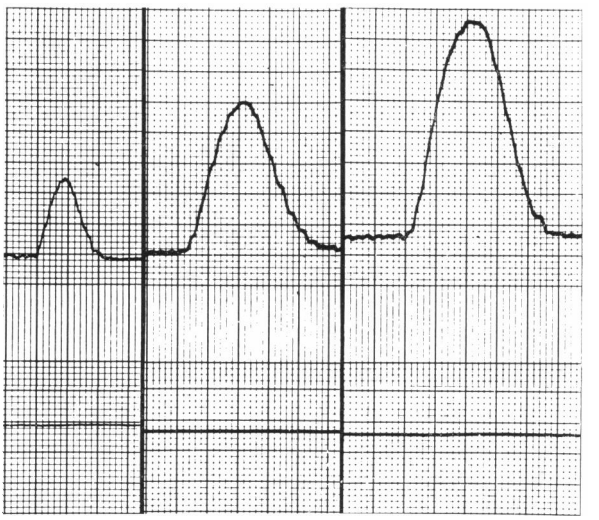

Fig. 13. Observations on an isovolumic preparation of the left ventricle similar to that shown in Figure 12 (from Figure 3 of Lendrum *et al.*[9]). Upper curves are pressure pulses from the isovolumically contracting left ventricle at different left ventricular volumes. The volumes of the ventricle were 15, 20, and 30 ml, respectively. The changes in diastolic pressure (0.3 and 10 mm. Hg) pulse height, peak pressure (40, 72, and 114 mm. Hg), and duration in the three panels are clearly evident. The absence of any change during systole in the lower trace, which is the pressure within the aorta, indicates the absence of systolic ejection, balloon protrusion or aortic valve regurgitation. Discussed in text.

because more of the ventricular effort goes to increase the pressure developed by the ventricle relative to the amount of the stroke output. This is true whether the cardiac input is fixed as in our experiments with the right heart bypass preparation or in the intact animal where the output of the heart can be modified by the afterload alteration.

Potentiation, as defined here, is a totally different phenomenon. It depends upon a change in the character of the contraction process that is independent of initial volume or afterload in that it will occur even when these latter do not alter. Potentiation may be produced by (sympathetic) nerve stimulation, by humoral agents transmitted to the heart in the blood, or it may be intrinsic in the myocardium without involving extrinsic factors. Excellent reviews on potentiation have recently appeared,[10, 11] but the phenomenon has been long established.[12-14] It has been shown to occur in isolated segments of atria and ventricles and in the isolated papillary muscle. Siebens *et al.*[15] have shown that it can occur in an isovolumically contracting right ventricle and Lendrum *et al.*, [16] in our department, have shown that it can occur in

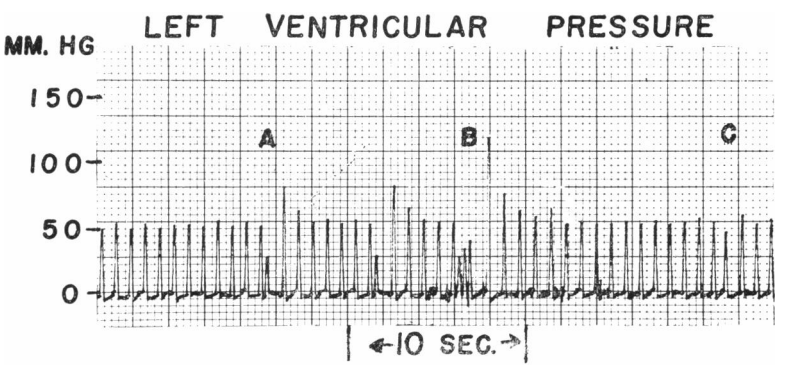

Fig. 14. Observations on an isovolumic preparation of the left ventricle similar to that shown in Figure 12 (from Figure 2 of Lendrum *et al.*[16]). In this slow speed record, the effects of spontaneous ectopic premature systole on ventricular potentiation are shown. *A* represents the pressure changes induced by an early premature systole (which is repeated several beats later); *B* represents the effect of a run of three premature systoles. Discussed in text.

the isovolumically contracting left ventricle (prepared as described above).

The form of potentiation that we are most interested in here, that due to premature beats, was studied extensively by Woodworth in 1902.[12] In our department, we established in the isovolumically contracting left ventricle[16] that:

1) Premature beats lead to potentiation of the following beat (Figure 14*A*)—except, on occasion, in interpolated ectopic beats where the postextrasystolic beat may, like the ectopic one, be diminished in size.

2) The earlier the premature beat occurs, the greater is the potentiation of the following beat (Figure 14*A* and *C*). The total area of the premature beat plus the one that follows it can become greater than twice the area of a single beat before the rhythm disturbance took place.

3) Potentiation can last over several successive beats (Figure 14).

4) A series of premature beats, as in a bigeminy, produces progressively more and more potentiation as the bigeminal rhythm continues (up to a point).

5) A succession of premature beats can produce a greater potentiation of the beat that follows than a single premature beat (Figure 14, compare *B* with *A*).

Enhancement of the effective beat with paired or coupled pacing was noted by Lopez *et al.*[2] (Figure 1) and also by Chardack's group,[3]

TABLE I—ISOVOLUMIC PREPARATION (AT CONSTANT END-DIASTOLIC VOLUME)

Expt. No. (date)	*Artif. Pac.*	*HR*	*ΔHR*	*CF*	*ΔCF*	*O_2C*	*ΔO_2C*	*EDP*	*O_2C per stroke*	*LV dp/dt*	*Area+ per cycle of Effective LV beats*	*Area+ per cycle of All LV beats*
1	Off	100	.....	66	.....	4.47	.....	15.0	.045	550	4.8	.....
(6/27/63)	On	60	-46	62	- 6	4.89	+0.80	15.0	.082	917	10.1	10.1
	Off	111	.....	71	.....	3.71	.....	15.0	.033	492	4.2	.....

Artif. Pac.—artificial pacemaker.
HR—heart rate (effective beats per minute).
ΔHR—change in rate of effective beats during artificial pacing.
CF—coronary flow per minute per 100 grams of heart weight.
ΔCF—change in coronary flow during artificial pacing.
O_2C—oxygen consumption of the heart in cc.s per minute per 100 gm. of heart weight.
ΔO_2C—change in oxygen consumption during artificial pacing.
EDP—end diastolic pressure of left ventricle in mm. Hg.
O_2C per stroke—oxygen consumption of the heart per stroke in cc. per 100 gm. of heart weight.
LV—left ventricle.
dp/dt—calculated as the ratio of the pressure rise in mm. Hg (during isovolumic contraction) to the duration of this phase in seconds.
+—area is expressed in $mm.^2$

TABLE II—CORONARY FLOW PREPARATION (RIGHT HEART BYPASS) WITH CONSTANT LEFT HEART INPUT DURING EACH EXPERIMENT

Expt. No. (date)	*Artif. Pac.*	*HR*	*ΔHR*	*CF*	*ΔCF*	*O_2C*	*ΔO_2C*	*EDP*	*O_2C per stroke*	*LV dp/dt*	*Area* per cycle of Effective LV beats*	*Area* per cycle of All LV beats*
2	Off	140	.....	38	.....	6.54	.....	5.0	.047	1231	2.7	2.7
(10/2/63)	On	100	-40	40	+ 1	7.05	+0.95	6.0	.070	1532	2.4	2.6
	Off	140	.....	40	.....	5.66	.....	11.0	.040	1040	2.3	2.3
3	Off	120	.....	31	.....	4.77	.....	-3.0	.040	1283	3.0	3.0
(10/7/63)	On	80	-40	37	+ 6	5.50	+0.73	-3.0	.069	1660	3.2	3.2
	On	80	-40	34	+ 3	4.88	+0.11	-5.0	.061	1925	3.3	3.3

	Off	115	.....	44	.....	5.90	.....	5.0	.051	810	2.5	2.5
	On	91	-22	53	+10	7.65	+2.02	4.0	.084	1251	2.7	2.7
4	On	*57	-56	47	+ 4	6.24	+0.61	6.0	.109	926	3.0	3.0
(11/13/63)	On	94	-19	45	+ 2	6.41	+0.78	4.0	.068	905	3.0	3.0
	Off	111	.....	42	.....	5.36	.....	5.0	.048	660	2.3	2.3
	On	*57	-54	49	+ 7	6.53	+1.17	6.0	.114	890	3.6	3.6
	Off	160	.....	29	.....	5.15	.....	4.3	.032	1088	2.4	2.4
	On	120	-44	36	+ 8	6.02	+1.36	5.0	.050	1500	2.3	2.6
	On	120	-44	38	+10	6.03	+1.37	5.0	.050	1375	2.4	2.8
5	Off	167	.....	28	.....	4.16	.....	5.0	.025	1034	2.4	2.4
(12/11/63)	On	100	-62	35	+ 7	5.11	+1.11	3.5	.051	1475	2.4	2.6
	On	100	-62	38	+10	5.28	+1.28	5.0	.053	1357	2.4	2.6
	Off	158	.....	29	.....	3.84	.....	4.0	.024	956	2.3	2.3
	On	91	-71	40	+ 6	4.68	+0.44	4.0	.051	1232	2.6	2.7
	Off	167	.....	40	.....	4.65	.....	6.0	.028	1071	2.2	2.2
	Off	167	.....	38	.....	6.95	.....	5.0	.042	897	2.6	2.6
	On	125	-42	45	+ 9	7.78	+1.06	5.0	.062	964	2.3	2.6
6	On	120	-47	42	+ 6	7.39	+0.67	5.0	.062	1000	2.2	2.5
(12/18/63)	Off	167	.....	35	.....	6.49	.....	10.0	.039	833	2.3	2.3
	On	100	-72	38	- 2	6.11	-0.50	9.0	.061	1150	2.5	2.6
	On	97	-75	46	+ 6	5.79	-0.82	9.0	.060	994	2.4	2.8
	Off	176	.....	46	.....	6.73	.....	6.0	.038	805	2.0	2.0
	On	94	-82	50	+ 4	6.82	+0.09	7.0	.072	1007	2.4	2.8
7	Off	125	.....	29	.....	4.35	.....	3.0	.035	588	2.3	2.3
(12/30/63)	On	79	-46	34	+ 5	4.78	+0.43	0	.060	597	2.5	2.5
	On	77	-48	42	+13	5.62	+1.27	-3.0	.073	614	2.2	2.2
8	Off	105	.....	38	.....	4.50	.....	6.0	.043	598	1.9	1.9
(2/11/64)	On	90	-15	44	+ 6	5.45	+0.95	5.0	.060	800	2.0	2.0
	On	60	-45	42	+ 4	4.53	+0.03	6.0	.076	926	2.5	2.5
9	Off	140	.....	41	.....	4.86	—	3.0	.035	654	2.5	2.5
(2/19/64)	On	120	-20	61	+20	6.96	+2.10	2.0	.058	844	1.7	2.4
11	Off	120	.....	42	.....	5.68	.....	9.0	.047	906	3.3	3.3
(2/24/64)	On	80	-40	50	+ 8	7.28	+1.60	10.0	.091	1450	3.3	3.3
12	Off	120	.....	59	.....	5.28	.....	-2.0	.044	1100	3.3	3.3
(11/30/64)	On	60	-60	64	+ 5	5.06	-0.22	-1.0	.084	1825	3.6	3.6
13	Off	100	.....	29	.....	4.40	.....	4.0	.044	711	4.3	4.3
(12/2/64)	On	60	-40	41	+12	6.30	+1.90	6.0	.105	1875	5.9	5.9
	On	60	-40	39	+10	6.32	+1.92	4.0	.105	1689	6.5	6.5

* Triads. See Table I for footnotes.

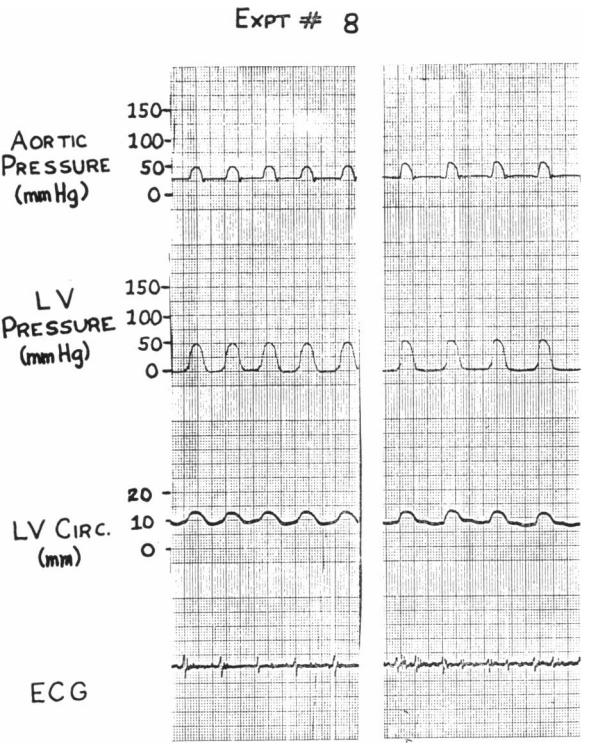

Fig. 15. Another experiment in the same type of preparation as in Figure 3 (from unpublished work of L. J. Hirsch and L. N. Katz). Conventions as in Figure 3. Left panel shows sinus rhythm (125/min.); the right panel paired artificial ventricular impulses that capture the ventricles, giving rise to alternating effective (90/min.) and ineffective beats. The latter do not appear in the aortic or left ventricular pressure pulses but do in the circumferential gauge. There is enhancement of the aortic pulse of the effective beats, an increase in dp/dt of the effective aortic and left ventricular pulses and an abbreviation of the duration of the pulse of the latter. No increase in left ventricular pulse is seen, and the summit changes from a dome before, to an earlier peak after paired impulses were acting. Discussed in text.

by Cranefield's group,[6] and by Braunwald's group.[4, 5] In all likelihood this enhancement is to be attributed to potentiation (as defined above) but it may be also due, in part at least, to augmentation (as defined above). There may be changes in heart size or coronary flow that can also contribute to the enhancement of the size of the effective beat (see below).

Hirsch and I have recently shown, in unpublished work, that paired pacing does lead to potentiation (Figure 12) in the isovolumic preparation of the dog. In the ordinary right heart bypass, which Hirsch and I have also studied, the *only* evidence of enhancement of the effective

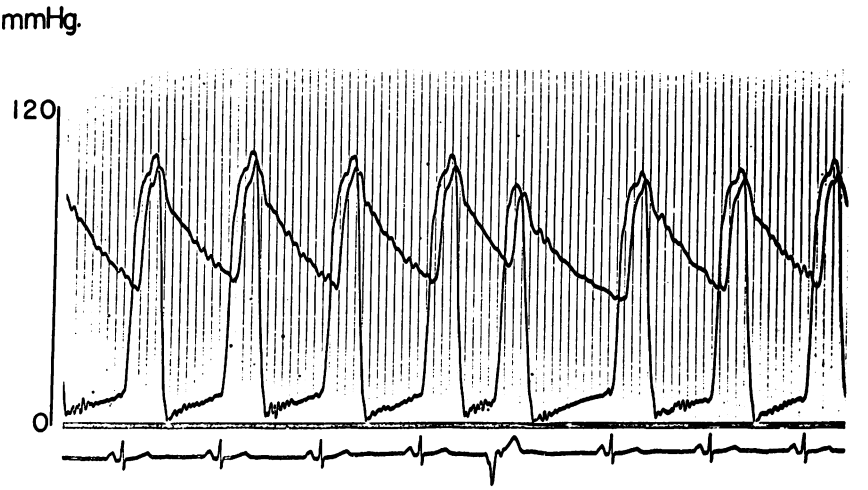

Fig. 16. A patient with a single (late diastolic) ventricular premature systole (with retrograde P wave). (Unpublished case of A. Shaffer.) The record shows the brachial and left ventricular pressure pulses and lead II. The pressure pulses engendered by the premature beat are smaller than the others and the postextrasystolic beat shows no enhancement. Discussed in text.

beat may be an increase in dp/dt (Table II); such an increase in dp/dt is also present when the beat is larger (Table II). It is also seen in the enhanced beat of the isovolumic preparation (Table I). The right heart bypass preparation employed by us prevented any change in cardiac minute-output and aortic blood pressure so that the size of the left ventricular pressure pulse of the effective beat was not increased at all (Figure 4, middle panel),[15] or only slightly (Figures 3, 4, right hand panel).[6, 11]

The effect of naturally occurring ectopic and premature beats in human cases are being analyzed by Shaffer of my department. A few examples can be shown here. Figure 16 shows the absence of any post-extrasystolic enhancement of the left ventricular pressure pulse because the ectopic beat is a late diastolic one. However, the brachial pulse pressure of this beat is lowered by the lengthened diastole preceding it.

Figure 10 shows two ectopic premature systoles, one interpolated and the other followed by a compensatory pause. It is the second beat after the first ectopic beat that shows an increase in both right ventricular and brachial pressure pulses. This same change is seen in the postextrasystolic beat after the second ectopic beat. Both ectopic premature beats are very early and hence would be expected to cause

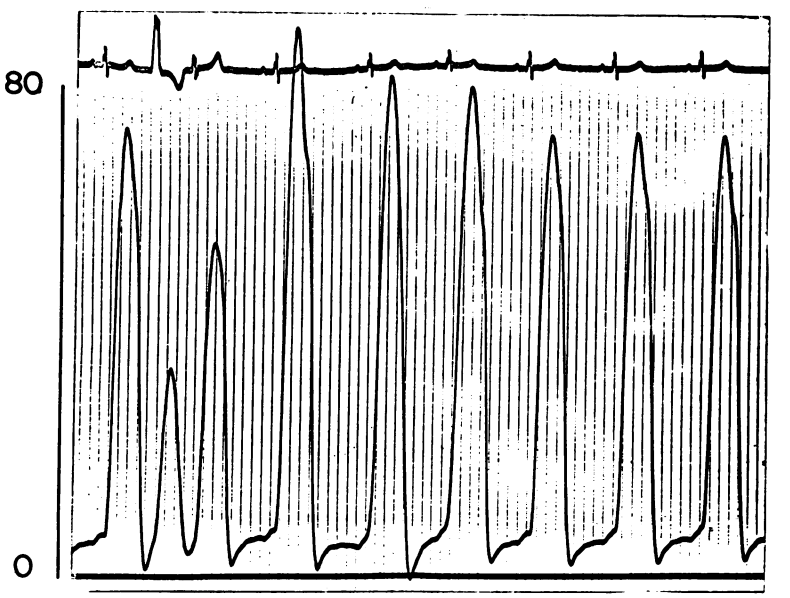

Fig. 17. A patient with a pair of premature beats (unpublished case of A. Shaffer). The record shows right ventricular pressure pulse (scale on left is in mm. Hg) and lead II. There is a sinus arrhythmia present. The first of the pair of premature beats is an ectopic ventricular systole. It may be interpolated with the following beat being sinus in origin with its P buried in the T of the preceding beat, its P-R prolonged, and showing some aberrant ventricular conduction. It is possible, instead, that this second beat is also ectopic in origin, arising near the septum, in which case there would be a pair of ectopic beats. In any event, the two premature beats have smaller than usual pressure pulses, and they are followed by three beats of enhanced size representing potentiation, at least in part. Discussed in text.

potentiation. There is also an increase in the atrial wave in the beats that are enhanced and this, added to the longer filling time preceding them, would contribute to the greater end-diastolic ventricular volume, and so cause augmentation.

Figure 17 shows a pair of early beats, the first (and perhaps both) of which are ectopic, which resulted in an increased height of the following three right ventricular pressure pulses, strongly suggesting potentiation.

Figure 18 shows an intermittent trigeminy due to interpolated ectopic premature systoles. The result was a *progressive* increase in the height of the beat that follows the pause, and also of the postextrasystolic beat and even of the premature ectopic beat. This too represents potentiation.

Increase in the height of the left ventricular pressure pulse of the postextrasystolic beat is also seen in Figure 19, a case with a significant

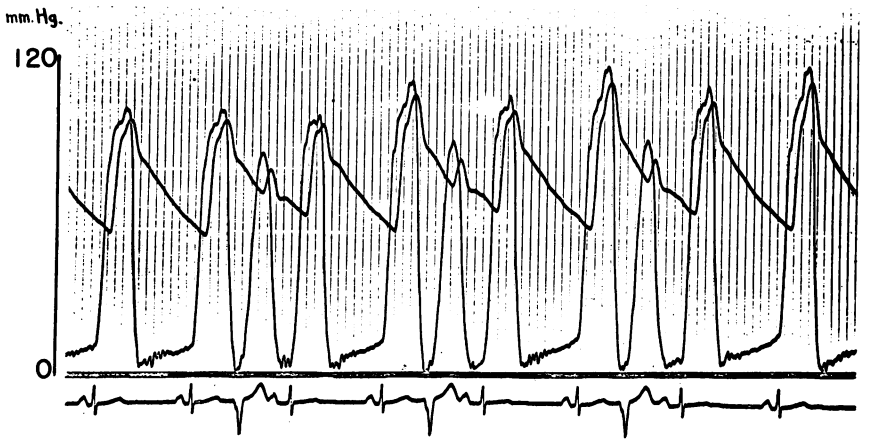

Fig. 18. A record taken on the same patient shown in Figure 16 when an intermittent trigeminy was present due to repetitive interpolated ventricular premature systoles (occurring earlier than in Figure 16). The several traces are the same as in Fig. 16. The premature beats are effective in that they each cause a small pulse in the brachial pressure curve as well as a smaller-than-usual pressure pulse in the left ventricle. The size of the ventricular pressure pulses that the premature systoles cause progressively increases as the trigeminy continues. The postextrasystolic beat after the first premature systole shows a decreased pulse in the brachial pressure curve and a slightly decreased one in the left ventricular pressure curve. Again, as the trigeminy continues, the postextrasystolic beat progressively increases in height. The second beat after the first premature systole shows definite enhancement of both the left ventricular and brachial pressure pulses, and this enhancement progresses as the trigeminy continues. The progressive enhancement of all three beats represents potentiation. Discussed in text.

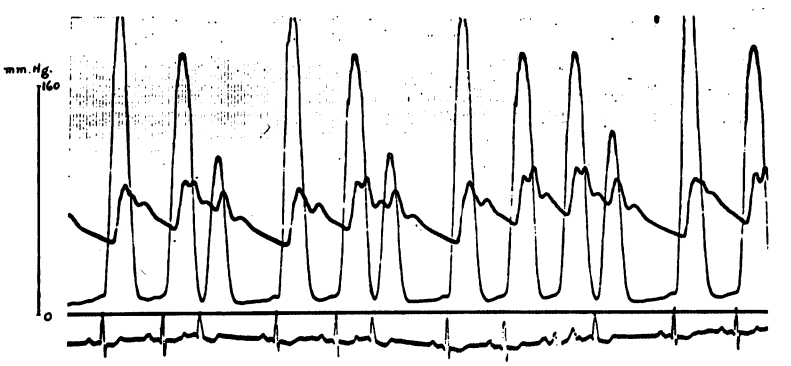

Fig. 19. A patient with significant aortic valve stenosis showing the effect of ventricular premature systoles—3d, 6th, 9th, and 10th ventricular complexes in lead II. (occurring pearlier than in Figure 16). The several traces are the same as in Fig. 16. brachial artery. The ninth beat is a late diastolic ectopic premature systole from a different focus than the other three. It does not significantly affect the pressure pulses. However, the other three premature beats all show a diminution in the pressure pulses and in each the postextrasystolic beat shows enhancement of the left ventricular peak systolic pressure accompanied by a fall in systolic pressure in the brachial pulse. The details of the effect of this fixed afterload are discussed further in the text.

aortic stenosis. While the pulse is increased in the brachial pressure curve of the postextrasystolic beat, this is due entirely to a drop of the diastolic pressure. While potentiation cannot be excluded in this case, the primary change is attributable to enhancement of the power of the postextrasystolic beat emptying through a more-or-less fixed narrow orifice, in which the capacity effect of the aorta and its major branches is markedly reduced insofar as buffering the systolic output of the left ventricle is concerned. This combination would prevent the stroke output from increasing as much as it would were the stenosis absent. Hence in this beat more of the heart's contractile force is expended in raising its cavitary pressure. In essence, there is a greater afterload in this beat, leading to augmentation.

A peculiar form of potentiation was seen in the patient whose records are shown in Figures 7 and 8, when paired pacing (lower panels) was substituted for single pacing (upper panels). The complete A-V dissociation was maintained and atrial systole continued to fall in different parts of the ventricular cycle. The effect of the varying atrial contribution, depending on where atrial contraction occurred in the ventricular cycle, was manifest as before in both the brachial and right ventricular pressure pulses. However, the amount of change in the pressure pulses due to the varying atrial contribution was greater when the paired impulses were used. It is our view that the difference between single and paired pacing in this case represents potentiation. This is explained by the fact that when the atrial contribution is most effective in filling the ventricles, the augmentation so produced not only magnifies the height of the pulse but also prolongs its duration. Hence the second artificial impulse comes to lie closer to the foot of the descent of the ventricular pressure pulse. This shift is clearly seen in the right ventricular pressure curve (Figure 7). By occurring closer to the preceding effective beat, the premature beat would lead to greater potentiation of the following effective beat. In this case, then, there is both augmentation due to the atrial contribution increasing ventricular volume and postextrasystolic potentiation, caused in this instance by the prolongation of the ventricular pressure pulse of the augmented beats which, in turn, is associated with a prolongation of the transmembrane action potential curve and the active state of the ventricles.

It is obvious from the foregoing presentation that the size of the effective beat is dependent upon a multiplicity of factors, not just one.

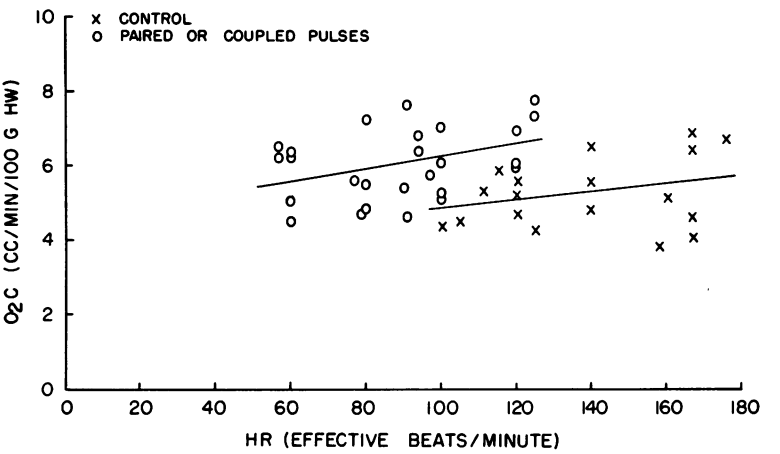

Fig. 20. A graph correlating cardiac oxygen consumption (O_2C) per min. (per gram of heart weight) to the heart rate (HR) of the effective beats in the dog's right heart bypass preparation (unpublished data of L. J. Hirsch and L. N. Katz). Data taken from Table II. There is a slight rise in O_2C with increasing heart rate (of effective beats) both when the heart is controlled exclusively by the sinus node *(X)* or paced by the paired or coupled artificial pacemaker *(O)*. However, the O_2C in the latter case is higher for any given rate of effective beats. With minute cardiac output maintained constant and aortic blood pressure varying little in any single preparation, this difference means that the mechanical efficiency of the external work of the heart is decreased when the paired or coupled stimuli were used. Discussed in text.

The Alteration in Oxygen Consumption of the Heart During Paired and Coupled Beating

When with paired or coupled artificial atrial stimulation the number of ventricular (electrical and mechanical) responses are reduced (Figure 2), the oxygen consumption of the heart per minute should be reduced. This change in minute oxygen consumption of the heart with heart rate was shown to occur by Laurent *et al.*[17] in my laboratory in the right heart bypass preparation when the minute cardiac output was fixed by maintaining a constant input to the left ventricle; the heart rate in these experiments was controlled by an artificial pacemaker giving rise to single impulses. Hirsch and I have obtained similar results over a narrower range of heart rates during normal pacing of the heart (Figure 20, *X*'s) in a similar preparation. The heart, therefore, does its external work more efficiently when its frequency is slower. The stroke oxygen consumption of the heart in Laurent's experiments did not change appreciably as the heart slowed so that the stroke work, which was increased, was also carried out more efficiently. This finding has been

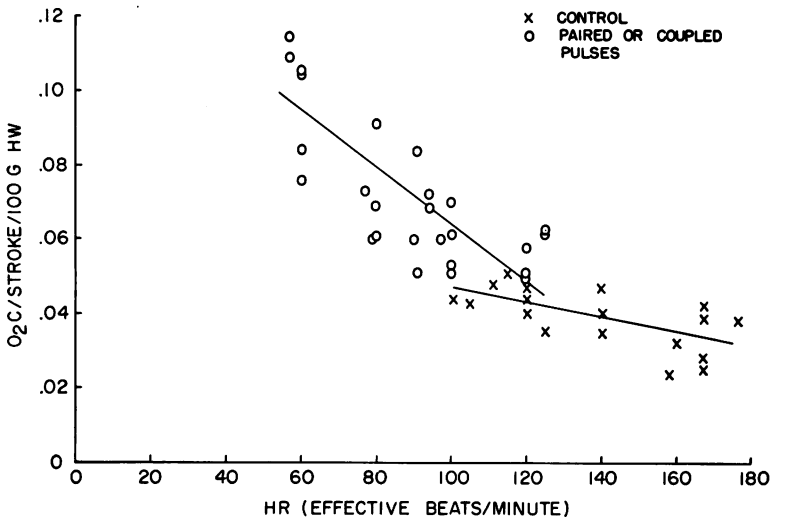

Fig. 21. A graph similar to Figure 20 and based on the same experiments but here the ordinates are O_2C per stroke (instead of O_2C per minute). There is only a slight change in O_2C per stroke when the heart is paced exclusively by the sinus node (X) but there is a sharp rise when paired or coupled artificial pacing is used as the effective heart rate slows *(O)*. How much of this change is due to the ineffective beat associated with the effective one, how much to the increased dp/dt of the effective beat, and how much is due to an improved state of the heart beat expressed in change in the heart size, for example, is not established. Discussed in text.

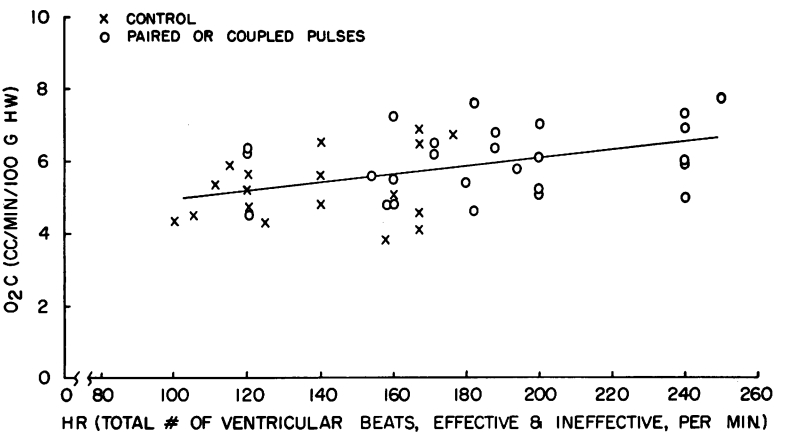

Fig. 22. Constructed as in Figure 20 except that here the abscissa represents total heart rate (effective plus ineffective ventricular beats per minute). It will be seen that a single regression line fits the data equally well, both the *X*'s and the *O*'s. This would suggest that the ineffective beats do consume a significant amount of oxygen. However, it does not exclude other factors acting on the effective beats and increasing the cardiac oxygen consumption. Discussed in text.

confirmed by Hirsch, Antic, and myself (unpublished data) and is seen also in Figure 21 (*X*'s).

With paired or coupled pacing, Braunwald's group[18] and Chardack's group[19] reported a variable effect on minute oxygen consumption of the heart in the closed-chested animal. Hirsch and I have recently examined this subject in the right heart bypass preparation with maintained constant minute output. The results are shown in Table II. By and large, the cardiac minute oxygen consumption increased when the artificial pacemaker was on, although the change was not statistically significant (Figure 20). A single regression line could reasonably represent the relation of the heart's minute oxygen consumption to the heart rate when the latter was calculated as the total of effective and ineffective beats (Figure 22). However, a different regression line was obtained for cardiac *stroke* oxygen consumption when paired and coupled beats were present than when they were absent (Figure 21).

When the reduction in frequency of the effective beats was plotted against the change in cardiac minute oxygen consumption between periods in which the artificial pacemaker was on and those when it was off, it was apparent that as the reduction in frequency of the effective beats increased, the increase in cardiac minute oxygen consumption tended to lessen (Figure 23). In fact, the cardiac minute oxygen consumption actually tended to fall when the slowing of frequency of effective beats was greatest. The wide scatter of points in this graph is due to the simultaneous operation of several factors, some of which act in opposite directions, namely:

1) The ineffective beats though isovolumic require the expenditure of energy and consumption of oxygen on the part of the heart. In our isovolumic preparation (see above), Lendrum *et al.*[9] showed clearly that there is a sizeable cardiac minute oxygen consumption even though the ventricle does no external work (see also Table I of the present report). This oxygen consumption varies with the magnitude of the pressure pulse of the left ventricle, here altered by changing the volume of this chamber (Figure 24). Therefore, it follows that the greater the ventricular pulse amplitude and area of the ineffective beats, the greater will be the cardiac minute oxygen consumption.

2) Any increase in the magnitude and area of the ventricular pressure curve of the effective beats, whether due to augmentation, potentiation, or both, will also lead to an increase in the minute oxygen con-

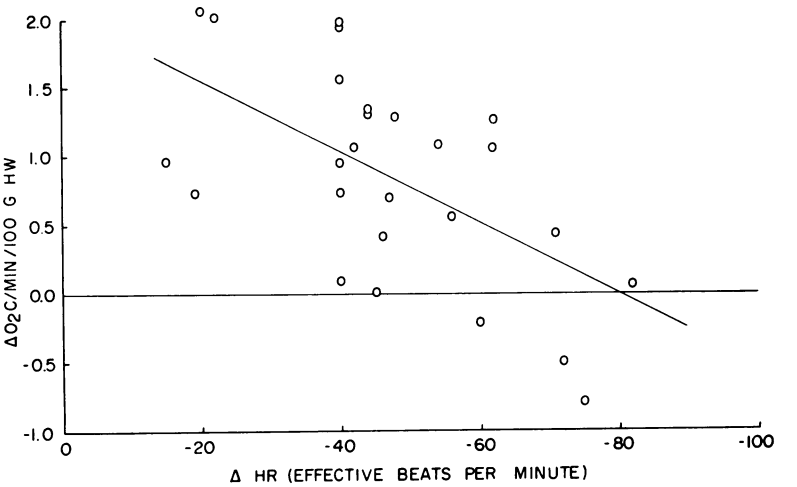

Fig. 23. A graph constructed from data in Table II, and shown in Figures 20 and 22, to compare the difference in cardiac oxygen consumption (ΔO_2C) per minute against the change in heart rate (ΔHR) of the effective ventricular beats per minute in individual experiments. It is clear that the greater the reduction in the number of effective beats per minute the smaller is the change in O_2C/minute. When the heart rate change is greatest, oxygen consumption (per minute) actually declines. The constructed line is the regression line for the widely scattered points. With cardiac output maintained constant in this preparation and mean aortic pressure varying little, it is apparent that *slowing of the heart rate* is a significant way of improving the mechanical efficiency with which the heart does its external work. This is one *consistent* benefit of coupled or paired pacing, provided the slowing is marked enough and the initial heart rate excessively rapid. Discussed in text.

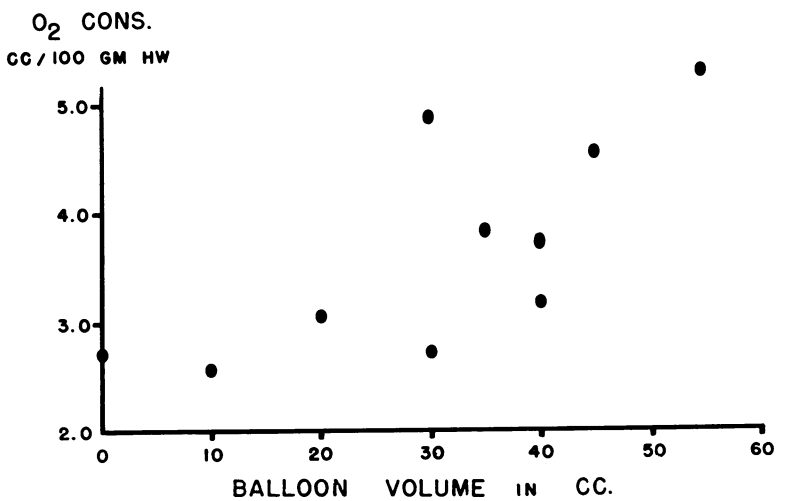

Fig. 24. Graph relating cardiac oxygen consumption to balloon volume within isovolumically contracting left ventricle (doing no external work and ejecting no blood) in the right heart bypass preparation of the dog (Figure 4 of Lendrum *et al.*[9]). Discussed in text.

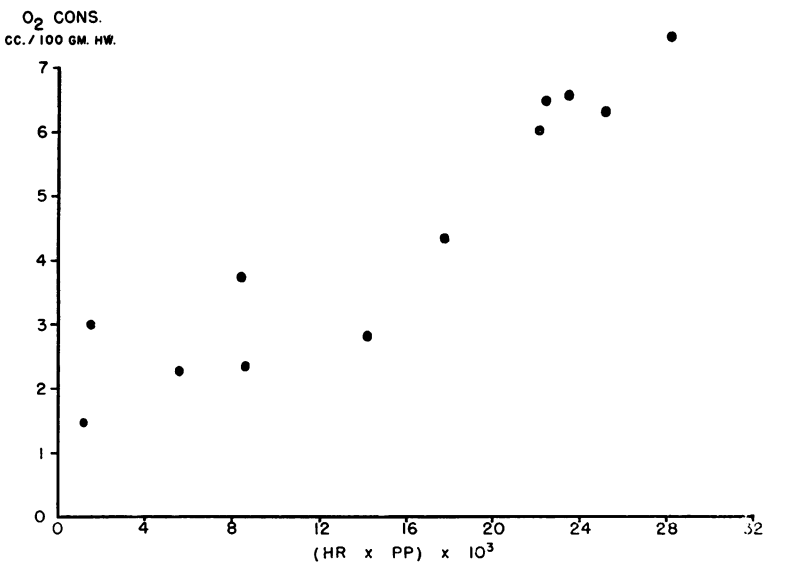

Fig. 25. Graph relating cardiac oxygen consumption to the product of heart rate (HR) and left ventricular pressure pulse amplitude (PP) in the same type of preparation used in obtaining Figure 24, in which the left ventricle contracts isovolumically and does no external work and ejects no blood (Figure 6 of Lendrum *et al.*[9] *Note:* 10^3 should read 10^{-3}.) Discussed in text.

sumption of the heart at any given heart rate. This is implicit in the results of Lendrum *et al.*[9] mentioned above. Hence the greater the ventricular pulse amplitude and area of the potentiated beat (as shown in Figure 12) the greater will be the cardiac minute oxygen consumption (Table I). This same effect would apply to the effective beat when the left ventricle is ejecting blood. However, in the right heart bypass preparation employed by Hirsch and myself, where the minute output was maintained constant and aortic pressure changed little, the area of the left ventricular pressure curve of the effective beat also changed little (Table II).

3) The frequency of the effective beats, as well as that of the ineffective ones, will also affect the minute oxygen consumption of the heart. In the naturally beating isovolumic preparation the cardiac oxygen consumption per minute was found to be a function of the product of heart rate and amplitude of the left ventricular pulse pressure (Figure 25). This correlation was also found when the systolic area of the pressure pulse was substituted for pulse amplitude.

The minute oxygen consumption of the heart in paired and coupled

beating, therefore, is determined by the sum of two products: 1) the amplitude times the frequency of the ineffective beats, and 2) the amplitude times the frequency of the effective beats. To this must be added a factor that is dependent upon the change in the rate of development of pressure in the isovolumic contraction phase of the effective beats, LV dp/dt of Table II, since this latter gives an added index of the character of the active state.

It is obvious from the foregoing that the *lower the frequency of the double beats, effective and ineffective, the lower will be the cardiac minute oxygen consumption. This needs emphasis.* On the other hand, the presence of the ineffective beat and the augmentation and potentiation of the effective one tend to raise the cardiac minute oxygen consumption.

When the maximum amount of coronary flow available to any part of the heart (or to the entire heart) becomes restricted by organic disease of the coronary vasculature, as in ischemic heart disease, then the possibility exists that the greater demands for oxygen per minute induced by paired or coupled beating (unless the heart rate is markedly reduced) will aggravate the insufficiency of coronary flow. The heart, therefore, will become a *poorer* and not a better *pump*. Furthermore, natural ectopic ventricular beats may also be engendered, and they, as well as the artifically paired or coupled impulses, can result in repetitive responses of the ventricles and ventricular fibrillation.

Alterations in Coronary Flow Following Paired and Coupled Beats

All the work of my department during the past few years has emphasized that coronary flow is *primarily* dependent upon the oxygen consumption of the heart, a view that is gaining wide acceptance. Coronary flow can be altered to some extent by external neurogenic and, to a greater extent, by external and intrinsic humoral changes as well as by the character of the heart's contraction and the magnitude of the driving pressure in the aorta, but the effect of these factors is much less than that controlled by the oxygen consumed by the heart. In fact, in many instances, these other determinants operate to a varying extent indirectly by changing the oxygen consumption of the heart. In paired coupled beating one would therefore expect that coronary flow alterations would roughly parallel the oxygen consumption of the

heart; that this actually occurred is shown in Table II. The lack of a better correlation is dependent upon the intervention of the other factors mentioned, aside from the errors in making the measurements of oxygen consumption and coronary flow.

Weisberg, Boyd, and I[20] have shown recently that when the coronary flow is low, it may limit the oxygen consumption of the heart and the magnitude of the heart's performance as indicated by the ventricular pressure pulse. This same finding was reported independently by Braunwald and his group.[21] It is possible, therefore, in the presence of such a critically low coronary flow to part of or to the whole heart, which can occur in ischemic heart disease and, possibly, also when the heart is greatly impaired following long-standing congestive heart failure, to mention two obvious states, that the performance of the heart and its oxygen consumption will be limited by the low coronary flow present. In the presence of such a state of affairs, the aim should be to improve the coronary flow rather than to use potentiation. The reason against the use of the latter is that potentiation would tend to aggravate the coronary insufficiency—for reasons outlined above.

An easy way of improving coronary flow under such conditions is to slow the heart rate, since in such slowing the duration of diastole, when coronary flow is more rapid, will be increased more than systole, when coronary flow is slower. The increased coronary flow so produced will permit a greater oxygen consumption per minute by the heart and a greater power of its beats. Congestion would consequently be relieved, the heart size would be reduced, and the heart would beat more effectively. Because its frequency is slower, the heart would perform its external work more efficiently and so require less oxygen per minute. In short, the ill effects of congestion, of dilation, of having the oxygen consumption and performance of the heart limited by the low coronary flow all would be overcome by raising coronary flow by slowing the heart rate. It is, therefore, essential to see that the total number of ventricular beats, both effective and ineffective, is reduced when this result is our aim. This means producing as marked a slowing of the heart rate as possible. If possible, atrial stimulation should be employed with the aim of *preventing the second beat of the pair or the coupled beat from reaching the ventricles*, as may be seen in Figure 2. Obviously atrial stimulation is useful in marked sinus tachycardia. It may be operative in other tachycardias of atrial origin but would not apply in

many instances to A-V junctional tachycardias and not at all to tachycardias of ventricular origin. It would also not work in atrial fibrillation and flutter.

So much interest in potentiation has developed recently that I am worried that the inherent benefits of simply reducing the total number of responses of the ventricle per unit of time will be overlooked.

Benefits to be Derived from Paired or Coupled Beats

There are a number of benefits to be derived per se from slowing of the frequency of the effective ventricular beats. They have been partly discussed in previous parts of this report. They may be summarized at this time as follows:

1) This procedure can overcome the reduced minute output of the heart and relieve the congestion of the heart and of its entering veins, a condition associated with the reduced filling time when the heart rate is excessively rapid, especially when the beats succeed each other in such quick succession as to fall in the rapid inflow phase. This situation arises especially in supraventricular paroxysmal tachycardia but may also be present in rapid ventricular response to atrial fibrillation and flutter, also in ventricular paroxysmal tachycardia. However, the question arises as to whether cardioversion may not be a better procedure to start with in a number of cases.

2) This procedure can increase coronary flow when coronary flow is the limiting factor that prevents the full release of energy by the heart as indicated by a restricted performance of the heart and a restricted rate of cardiac oxygen consumption. In this way, the performance of the heart is enhanced as the coronary flow improves. Improvement of coronary flow with slowing of the heart rate also tends to lessen the development of coronary flow insufficiency and thus the discomfort, the angina pectoris, the extension of myocardial infarction, and the heart failure that otherwise might develop.

3) This procedure can overcome the mechanical disadvantage of a dilated heart when it is present. This geometric handicap will be overcome when congestion of the heart is lessened as the improved emptying of the heart reduces the systolic residue within the ventricles.

In all the above, it would appear best to slow the total number of beats of the ventricles, both effective and ineffective. This is best accomplished by using atrial stimulation so arranged that only the first

of the pair of impulses reaches the ventricles but not the second impulse. Alternatively, it can be accomplished by employing atrial beats coupled to the ventricular response that in turn fail to capture the ventricles. In both cases, the ventricular frequency will be reduced both as regards mechanical and electrical responses.

The application of this atrial approach only to marked sinus tachycardia and atrial tachycardias other than atrial fibrillation and flutter has already been mentioned.

When ventricular application of the paired or coupled pacemaker must be used, the aim should be to reduce the total number of ventricular beats per minute, effective and ineffective, as much as possible. Slowing of total heart rate may be as important if not more important than potentiation. The limit of heart-rate slowing is set by the capacity of the effective beats to respond to augmentation. Ordinarily this would mean a frequency of effective beats of no less than 40/min. When the power of the heart is greatly reduced, obviously, the frequency limit will become higher than this. In fact, a rapid rate, up to 120, may be essential in order to maintain the minute output of the heart. It is when such marked impairment of the heart is present that potentiation becomes valuable.

The possibility of using not one but two, or even more, early impulses in the atria to increase the chance of causing ventricular slowing of electrical as well as mechanical beating (without causing atrial flutter and fibrillation) is being undertaken in the dog by Hirsch and myself.

There is an advantage, when using paired responses of the ventricles, to maintain an atrial contribution just before the effective ventricular beat occurs. This is discussed further by Dr. Langendorf. By using proper coupling, the augmentation of the ventricular beats by an effective atrial contribution properly timed before the effective ventricular beat will be increased and thus ensure more complete emptying of the blood coming to the heart. Placing an effective atrial beat before the effective ventricular one may be more important than potentiation of the ventricular beat; perhaps as important as reducing the total number of ventricular beats per minute.

Finally, the added advantage of postextrasystolic potentiation by properly placed ventricular ineffective beats with paired or coupled impulses has been considered in this report. There is still doubt in my

mind whether the hazards associated with paired ventricular responses unaccompanied by significant slowing of the total ventricular beats per minute do not ordinarily outweigh the benefits to be derived from augmentation and potentiation in a seriously diseased heart. The case illustrated in Figure 5, mentioned earlier, is a case in point. Here ventricular fibrillation occurred, and countershock had to be used to break this serious complication. In this patient with severe congestive heart failure, Shaffer, Luria, and Langendorf found that the cardiac output before using paired ventricular pacing was 1.3 l./min. and that after pacing it rose to 2.3 l./min. The rate of the effective heart beats was 100/min. before and 70 after pacing, so that the stroke output increased from 13 ml. to 30 ml./stroke. The above values are to be considered only as rough approximations, since dye curves obtained with such low cardiac outputs cannot be calculated accurately. Apparently potentiation of the heart's performance was accomplished in this case, but only with the associated risk, which became an actuality, of developing ventricular fibrillation.*

Conclusion

I shall not attempt to summarize our experience as expressed in this report, but I should like to conclude by saying that the problem is not as simple as one might wish. There are still many gaps to be filled; the information with which to fill some of them will be supplied, I hope, by other contributors to this symposium. Until they are, this exciting new way of improving the performance of the heart is to be considered a tool that should be limited to the most sophisticated cardiologists who have due appreciation of the indications and hazards involved.

* In our human work, we have employed a battery-operated transistorized pacemaker. When a pacemaker is operated off the regular electrical lines, special precautions to ensure proper insulation are required.

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